

REMARKS

Claims 1-36 will be pending upon entry of the presently made amendments. Claims 3-21, 24, 25 and 36 are withdrawn from consideration as being drawn to a non-elected invention.

Claims 30 and 31 have been amended to correct an inadvertent typographical error with respect to the spelling of the term “wherein.” Claim 31 has been further amended to correct an inadvertent typographical error with respect to the spelling of the term “dystonia” and to depend from claim 1.

No new matter has been added.

Applicants reserve their right to prosecute the subject matter of any canceled claim, any amended claim, any withdrawn claim or any unclaimed subject matter in one or more divisional, continuation or continuation-in-part applications.

I. The Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1, 2, 22, 23 and 26-35 are rejected under 35 U.S.C. § 112, first paragraph. In particular, while acknowledging that the specification is enabling for the treatment of pain, the Examiner has stated that it does not reasonably provide enablement for the prevention of pain. Applicants respectfully traverse this rejection.

The Examiner has stated that all of the guidance and working examples provided by the specification are directed towards treatment rather than prevention of pain. Applicants respectfully disagree. Indeed, each of the examples in Sections 5.1-5.4 at pages 67-70 are directed to the prevention of pain. In particular, each example teaches that the JNK inhibitor is administered prior to the inducement of pain (*e.g.*, by formalin injection, hot plate, tail-flick or topical capsaicin). Applicants submit that these animal models reasonably enable one skilled in the art to test a compound for its ability to prevent pain. Accordingly, Applicants respectfully submit that these examples rebut the Examiner’s assertion that it would require undue experimentation to practice the claimed invention to prevent pain because one skilled in the art would have to envision an appropriate animal model.

The Examiner has further stated that one skilled in the art would have to envision an appropriate pharmaceutical carrier, compound dosage, duration of treatment, route of administration, etc. Applicants respectfully submit that the Federal Circuit has held that a specification is enabling in part because those skilled in the art would know how to conduct a

dose response study to determine the appropriate amounts to be used. *Merck & Co., Inc. v. Biocraft Laboratories, Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989).

The Examiner has further pointed to the lack of guidance from the specification and prior art with regard to the actual prevention of pain in a human subject with the claimed compounds. Applicants respectfully submit that Title 35 does not demand the development of such therapeutic regimens or that any human testing occur within the confines of Patent and Trademark Office proceedings. *In re Brana* at 1567 (Testing for the full safety and effectiveness ... is more properly left to the Food and Drug Administration (FDA)). This regulatory process is not the same as the enablement requirement under 35 U.S.C. § 112, first paragraph. In other words, neither human testing nor FDA approval are prerequisites to patentability.

Applicants respectfully submit that claims directed to the prevention of pain are reasonably enabled by the specification as filed in view of its teaching of numerous JNK inhibitors and of multiple animal models useful for demonstrating the ability of a compound to prevent pain.

Accordingly, Applicants submit that the rejection of claims 1, 2, 22, 23 and 26-35 under 35 U.S.C. § 112, first paragraph, has been overcome and should be withdrawn.

II. The Rejection Under 35 U.S.C. § 102(e) over U.S. Patent No. 6,897,231 B2

Claims 1 and 28-35 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,897,231 B2 to Bhagwat *et al.* (the “’231 patent”). Applicants respectfully traverse this rejection.

The Examiner’s position appears to be that the teaching of the ’231 patent of the treatment of certain diseases (*i.e.*, stroke, asthma, osteoarthritis, rheumatoid arthritis, lupus erythematosus, diabetes and cancers of a variety of tissues) with the compounds of the present method claims necessarily teaches the prevention or treatment of pain associated with the diseases. In other words, Applicants understand the Examiner to be arguing that treatment of a certain disease necessarily treats the pain associated with the underlying disease. Applicants respectfully submit that this is not the case.

The current paradigm in clinical pain management recognizes that it is essential to differentiate etiological factors or disease/causative factors from pain mechanisms themselves. *See* second paragraph at page S142 of Woolf and Decosterd, 1999, “Implications of recent advances in the understanding of pain pathophysiology for the assessment of pain in patients,” *Pain Supplement 6*:S141-S147 (enclosed herewith as reference C01). In other

words, treatment of an underlying condition is unlikely to prevent or treat pain associated with the condition and, in fact, disease-based classification for treating pain is discouraged. See second paragraph at page S142 of Woolf and Decosterd. Indeed, it is now recognized that the pain itself is the disease. See second full paragraph at page S145 of Woolf and Decosterd; and last sentence of “Summary” at page 31 of R.A. Sternbach, 1981, “Chronic Pain as a Disease Entity,” *Triangle* 20(1/2):27-30 (enclosed herewith as reference C02). Accordingly, Applicants believe that the pending claims are indeed directed to novel methods of use and do not read upon the subject matter of the '231 patent.

As discussed above, the current scientific literature teaches that pain mechanisms are unique and not associated with the etiology of an underlying condition. Applicants submit that phantom limb pain is an especially useful example for illustrating the disconnect between an underlying condition and pain itself. Specifically, it is well documented that many amputees experience the persistence of severe pain in their missing limb. See first sentence at page 57 of N. Postone, 1987, “Phantom Limb Pain. A Review,” *Int'l. Psychiatry in Medicine* 17(1):57-70 (enclosed herewith as reference C03). In fact, such pain may arise even up to 15 years after amputation (*i.e.*, long after any injury has healed). *Id.* at last full sentence at page 59. The fact that a person can experience severe pain in a body part no longer present clearly illustrates that pain is distinct from any underlying condition.

Other illustrative examples wherein treatment of an underlying condition will not necessarily treat the associated pain include cancer and inflammatory diseases. In such cases, a tumor or inflammation can trigger a pain mechanism causing the pain to persist even after the tumor or inflammation is no longer present. For example, chronic pain is often seen in post thoracotomy and post mastectomy syndromes, and sympathetically maintained pain has been documented in connection with certain paraneoplastic syndromes (*e.g.*, carcinoma of the prostate, breast, lung, brain and gynecologic tumors). See second full paragraph at page 308 and fourth full paragraph at page 313 of Wilsey *et al.*, 2001, “A Review of Sympathetically Maintained Pain Syndromes in the Cancer Pain Population: The spectrum of ambiguous entities of RSD, CRPS, SMP and other pain states related to the sympathetic nervous system”, *Pain Practice* 1(4):307-323 (enclosed herewith as reference C04).

Without being limited by theory, it is postulated that such pain is maintained independently from the underlying condition due to one or more of: (i) reductions in the threshold to firing of second-order neurons in the spinal dorsal horn; (ii) increases in responsiveness of the neurons to nociception; (iii) after-discharging or spontaneous neuronal

signaling; and (iv) spreading of sensitivity to adjacent neurons in the dorsal horn. *See* third full paragraph at page 308 of Wilsey *et al.*

Applicants respectfully submit that the literature references and examples discussed above demonstrate that pain and any underlying condition are separate entities with respect to their treatment and that pain itself should be considered as a disease in its own right. Thus, Applicants respectfully submit that the pending claims are indeed directed to novel methods of use and do not read upon the subject matter of the '231 patent.

Accordingly, Applicants submit that the rejection of claims 1 and 28-35 under 35 U.S.C. § 102(e) has been overcome and should be withdrawn.

III. The Rejection Under 35 U.S.C. § 102(e) over U.S. Patent No. 6,897,231 B2 Evidenced by U.S. Patent No. 5,766,605 or U.S. Patent No. 5,434,136

Claims 1 and 28-31 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by the '231 patent evidenced by U.S. Patent No. 5,766,605 A to Sanders *et al.* (the "'605 patent") or U.S. Patent No. 5,434,136 A to Mathias (the "'136 patent"). Applicants respectfully traverse this rejection.

Applicants respectfully submit that autonomic dysfunction can be a component of certain diseases but is not a type of disease as implied by the Examiner. As discussed below, Applicants respectfully submit that asthma and lupus erythematosus are not "autonomic dysfunctions."

The Examiner has stated that the '605 patent teaches in the abstract and claim 1 that asthma is an autonomic dysfunction. Applicants respectfully disagree and submit that the '605 patent teaches that the function of an autonomic nerve can contribute to a symptom of asthma. In other words, asthma is not an autonomic dysfunction but can have an autonomic nerve component.

The Examiner has further stated that the '136 patent teaches at column 1, lines 11-20 that lupus erythematosus is an autonomic dysfunction. Applicants respectfully disagree and submit that the '136 patent teaches that lupus erythematosus is an autoimmune disease which can have an autonomic dysfunction component.

Applicants respectfully submit that a teaching of the treatment of one disease having autonomic dysfunction as a component does not anticipate the treatment of a different disease which has an autonomic component and, accordingly, the teachings of the '605 patent and the '136 patent do not anticipate the present claims. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987).

Accordingly, Applicants submit that the rejection of claims 1 and 28-31 under 35 U.S.C. § 102(e) has been overcome and should be withdrawn.

IV. The Rejection Under 35 U.S.C. § 102(e) over U.S. Patent Application Publication No. 2004/0067953 A1

Claims 1 and 28-31 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent Application Publication No. 2004/0067953 A1 to Stein *et al.* (the “’953 publication”). Applicants respectfully traverse this rejection.

As discussed above, the treatment of an underlying condition and pain associated with the condition are separate and distinct. With respect to cancer, as discussed above, Applicants note that the enclosed literature reference by Wilsey *et al.* teaches that cancers and tumors can cause persistent pain states with mechanisms that are unrelated to the etiology of the underlying condition. Thus, a teaching of the treatment of cancer does not anticipate the treatment of pain associated with cancer.

Accordingly, Applicants submit that the rejection of claims 1 and 28-31 under 35 U.S.C. § 102(e) has been overcome and should be withdrawn.

V. The Rejection Under 35 U.S.C. § 103(a) over U.S. Patent Application Publication No. 2004/0067953 A1

Claims 1, 2, 22, 23 and 26-35 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the ’953 publication in view of PCT International Publication No. WO 02/081475 A1 to Graczyk *et al.* (the “’475 publication”). Applicants respectfully traverse this rejection.

Applicants respectfully submit that the ’953 publication is only available as prior art to the present application under 102(e)/103. In particular, the present application has a priority date of October 24, 2002 and the ’953 publication was published on April 8, 2004.

Accordingly, Applicants respectfully submit that the ’953 publication is disqualified as prior art pursuant to 35 U.S.C. § 103(c) as amended by the CREATE Act because the subject matter of the ’953 publication and the claimed invention were, at the time the claimed invention was made, owned by the same person or organization or subject to an obligation of assignment to the same person or organization. In particular, Applicants respectfully state that at the time the claimed invention was made, the underlying application of the ’953 publication was owned by or subject to an obligation of assignment to Signal Pharmaceuticals, LLC (a wholly owned subsidiary of Celgene Corporation) and the presently claimed invention was subject to an obligation of assignment to Celgene Corporation.

Accordingly, Applicants submit that the rejection of claims 1, 2, 22, 22 and 26-35 under 35 U.S.C. § 103(a) has been overcome and should be withdrawn.

Conclusion

Applicants respectfully request that the above remarks be entered in the present application file. No fee is estimated to be due in connection with this Response; however, in the event that any fee is due, please charge the required fee to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

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